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Published in:
Neurobiology of Aging

DOI:
10.1016/j.neurobiolaging.2019.10.004

Publication date:
2020

Licence:
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Document Version
Peer reviewed version

Link to publication in Discovery Research Portal

Citation for published version (APA):
Benwell, C. S. Y., Davila-Perez, P., Fried, P. J., Jones, R. N., Travison, T. G., Santarnecchi, E., Pascual-Leone, A., & Shafi, M. M. (2020). EEG spectral power abnormalities and their relationship with cognitive dysfunction in patients with Alzheimer's disease and type 2 diabetes. *Neurobiology of Aging*, *85*, 83-95. https://doi.org/10.1016/j.neurobiolaging.2019.10.004

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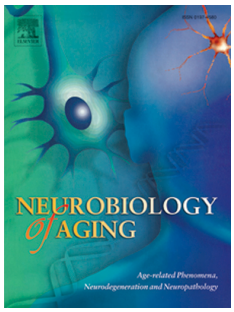

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PII: S0197-4580(19)30359-8

DOI: https://doi.org/10.1016/j.neurobiolaging.2019.10.004

Reference: NBA 10686

To appear in: *Neurobiology of Aging*

Received Date: 24 July 2018

Revised Date: 30 September 2019

Accepted Date: 7 October 2019

Please cite this article as: Benwell, C.S.Y., Davila-Pérez, P., Fried, P.J., Jones, R.N., Travison, T.G., Santarnecchi, E., Pascual-Leone, A., Shafi, M.M., EEG spectral power abnormalities and their relationship with cognitive dysfunction in patients with Alzheimer's disease and Type 2 Diabetes, *Neurobiology of Aging* (2019), doi: https://doi.org/10.1016/j.neurobiolaging.2019.10.004.

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Abstract

Rhythmic neural activity has been proposed to play a fundamental role in cognition. Both healthy and pathological aging are characterized by frequency-specific changes in oscillatory activity. However, the cognitive relevance of these changes across the spectrum from normal to pathological aging remains unknown. We examined electroencephalography (EEG) correlates of cognitive function in healthy aging and two of the most prominent and debilitating age-related disorders: Type-2 diabetes mellitus (T2DM) and Alzheimer's disease (AD). Relative to HC, AD patients were impaired on nearly every cognitive measure, while T2DM performed worse mainly on learning and memory tests. A continuum of alterations in resting-state EEG was associated with pathological aging, generally characterized by reduced alpha (α) and beta (β) power (AD<T2DM<HC) and increased delta (δ) and theta (θ) power (AD>T2DM>HC), with some variations across different brain regions. There were also reductions in the frequency and power density of the posterior dominant rhythm in AD. The ratio of (α+β)/(δ+θ) was specifically associated with cognitive function in a domain- and diagnosis-specific manner. The results thus captured both similarities and differences in the pathophysiology of cerebral oscillations in T2DM and AD. Overall, pathological brain aging is marked by a shift in oscillatory power from higher to lower frequencies, which can be captured by a single cognitively relevant measure of the ratio of (α+β) over (δ+θ) power.

Keywords

Cognitive aging, Type-2 diabetes mellitus, Alzheimer's disease, EEG, Oscillations, Neuropsychology

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Introduction

Some subtle neurocognitive changes occur with normal aging (Harada et al., 2013), while others are more severe and associated with specific pathophysiological processes. The most extreme example is dementia due to Alzheimer's disease (AD). AD is associated with progressive alterations including the accumulation of beta-amyloid plaques and neurofibrillary tangles, cortical hypometabolism, and eventually widespread atrophy (Braak and Braak, 1998; Jack et al., 2013). Among AD risk factors (Burns and Iliffe, 2009), one of the most prominent is Type-2 Diabetes Mellitus (T2DM) (Biessels and Kappelle, 2005). T2DM is a chronic metabolic disorder characterized by abnormal glucose metabolism and insulin resistance, and is associated with myriad physiological complications, including in the central nervous system (CNS) (Alberti and Zimmet, 1998; Awad et al., 2004; Biessels and Kappelle, 2005; Gispen and Biessels, 2000; Koekkoek et al., 2014; Roberts et al., 2014; Saedi et al., 2016; Stewart and Liolitsa, 1999; Strachan et al., 2011). Mild deficits in memory, executive function and perceptual processing speed have been observed in T2DM (Cheng et al., 2012; Marseglia et al., 2016; Mooradian et al., 1988; Palta et al., 2014; Takeuchi et al., 2012; van den Berg et al., 2010). While the impact of T2DM on the CNS is likely multifactorial, microvascular damage and impaired insulin signaling have been identified as probable mediators in the higher risk for AD and vascular dementias (Biessels et al., 2014; Ohara, 2011; Toth, 2014). However, understanding of how T2DM fits into the spectrum from normal cognitive aging to AD remains incomplete (de la Monte, 2014).

Electroencephalography (EEG) permits noninvasive measurement of temporally synchronized (i.e., oscillatory) neural activity, a ubiquitous characteristic of the brain (Buzsaki et al., 2013) which has been proposed as a mechanism for encoding and transfer of information (Bonnefond et al., 2017; Fries, 2015). These proposals are based on reliable associations between frequency-specific oscillations and various cognitive functions (Ward, 2003), as well as their implication in various neuropsychiatric disorders (He et al., 2007; Oswal et al., 2013;

Schnitzler and Gross, 2005; Uhlhaas and Singer, 2006). Systematic changes in neural oscillations occur with normal cognitive aging (Babiloni et al., 2006b; Marshall and Cooper, 2017; Rossini et al., 2007; Stomrud et al., 2010; Vlahou et al., 2014). For instance, alpha-band (8-13 Hz) activity decreases in both amplitude (Babiloni et al., 2006b; Marshall and Cooper, 2017) and peak frequency (Klimesch, 1999; Mierau et al., 2017; Knyazeva et al., 2018) throughout adulthood. However, changes in lower frequency (<8 Hz) activity, and the relationship with cognitive function, appear to be less consistent (Babiloni et al., 2006a; Cummins and Finnigan, 2007; Klass and Brenner, 1995; Leirer et al., 2011; Marshall and Cooper, 2017).

Oscillatory abnormalities have been consistently observed in pathological aging (Assenza et al., 2017; Babiloni et al., 2004, 2006a; Fraga et al., 2013; Neto et al., 2016; Voytek and Knight, 2015). In AD, the most prominent EEG finding is a shift in power from higher to lower frequencies: an increase in power in delta (δ; 1-4 Hz) and theta (θ; 4-8 Hz) frequency bands, and a concomitant decrease in power in alpha (α; 8-13 Hz) and beta (β; 13-30 Hz) bands, along with reduction of the individual peak α frequency (Babiloni et al., 2004; Bennys et al., 2001; Brenner et al., 1986; Coben et al., 1983; Moretti et al., 2004). The relationship between these oscillatory changes and cognitive dysfunction remains unclear, though some studies have reported correlations with individual tests of cognitive functions (Babiloni et al., 2007; Moretti et al., 2009; van der Hiele et al., 2007). While fewer studies have examined oscillatory changes in T2DM, there is some evidence of a similar shift in power from higher to lower frequencies (Bian et al., 2014; Cooray et al., 2011; Cui et al., 2014; Wen et al., 2016; Zeng et al., 2015).

The aim of the current study was to compare resting-state EEG oscillatory activity, and its relationship with neuropsychological function, across healthy and pathological aging (T2DM and AD). We hypothesized that neuropsychological testing and resting-state oscillatory activity would reveal a pattern of neurocognitive dysfunction from healthy controls (HC) to T2DM to AD. Additionally, we predicted that resting-state EEG measures (i.e. power density and peak

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frequencies) would be associated with domain-specific cognitive performance both within and across groups, with AD showing the strongest relationships (Babiloni et al., 2018, 2015).

Methods and Materials

Human Participants

This is an analysis of 72 adults who participated in research at the Berenson-Allen Center for Noninvasive Brain Stimulation at Beth Israel Deaconess Medical Center between 2012 and 2015. The local Institutional Review Board approved the study. All participants provided written informed consent prior to enrollment according to the Declaration of Helsinki. Participants were drawn from the following groups:

Alzheimer's disease. 18 participants (11 females, aged 52-86) with a probable diagnosis of mild-to-moderate AD according to DSM-V/NINCDS-ADRDA criteria (McKhann et al., 2011), with a clinical dementia rating (CDR) of 1.0 and a mini-mental status exam (MMSE) (Folstein et al., 1975) score between 18-24. Six patients were medicated with Cholinesterase inhibitors, nine were on Cholinesterase inhibitors and Memantine, while 3 were not taking dementia-specific medications.

Type-2 diabetes mellitus. 27 participants (12 females, aged 50-78) had a clinical diagnosis of T2DM, and had normal cognition as indicated by a MMSE score ≥ 27 (Rosa et al., 2018), with no subjective cognitive complaints. All had their diabetes at least moderately controlled (hemoglobin A1c; HbA1c < 10) through some combination of diet, exercise, Metformin, insulin, or insulin homologues.

Healthy control. 27 participants (13 females, aged 50-77) had normal cognition (MMSE ≥ 27) and glucose metabolism (HbA1c < 6.5%).

General inclusion criteria included: age-adjusted score ≥ 80 on the 50-item Wechsler Test of Adult Reading (W-TAR; as a surrogate measure of premorbid IQ); no other unstable medical or neuropsychiatric conditions (apart from AD or T2DM). All participants underwent

equivalent testing, including a structured neurological exam, medical history review, formal neuropsychological testing, and an EEG visit. Participant characteristics (**Supplementary Table S1**), including age, education, and premorbid IQ, were compared across groups using one-way analyses of variance (ANOVAs) with Tukey's Honestly Significant Difference (HSD) post hoc comparisons. MMSE scores were compared using a non-parametric Kruskal-Wallis test. Gender proportions were compared using Fisher's Exact Test. As the AD group was significantly older, *Age* was added as a covariate to all subsequent between-group analyses. Additionally, to verify that the main results were not confounded by between-group age differences, we reran several of the primary analyses on a cohort of 17 age-matched participants per group (see Supplementary Material for more details).

This and all subsequent analyses were performed in JMP Pro (v12.0, http://www.jmp.com) using a normal distribution and a two-tailed 95% confidence interval.

Neuropsychological testing

Neuropsychological testing was performed on a separate visit from the EEG recording by a trained psychometrist. Tests and inventories were drawn from the National Alzheimer's Coordination Center's Uniform Data Set version 1.1 (NACC-UDS) (Beekly et al., 2007). The following neuropsychological tests were employed: the 15-item Geriatric Depression Scale (GDS); a 23-item Activities of Daily Living inventory (ADLs); the Digit Symbol Substitution Test (DSST; number of correct substitutions in 90 sec); Digit Span Forward and Backward tasks (longest set length repeated); the Logical Memory, Story-A (number of items recalled immediately and after a 30-minute delay without cueing) from the Wechsler Memory Scale-Revised; the Trail Making Test (difference in time and in errors between parts B and A; TMT_{B-A}) from the Halstead-Reitan Battery; the "animals" category of the Semantic Fluency Test (number of unique words generated in one min); and the 30-item Boston Naming Test (number of correctly named objects with semantic cue). In addition, the 70-item Cognitive subscale of the

158 Alzheimer's disease Assessment Scale (ADAS-Cog) (Mohs et al., 1983) was administered to
159 measure global cognitive function, and a 10-item version of the Rey Auditory Verbal Learning
160 Test (RAVLT; percent correct during learning, 20-min delayed recall, and delayed recognition
161 trials) (Rosenberg et al., 1984) was administered to further probe verbal learning and memory
162 ability (Calero and Navarro, 2004). All measures were Z-transformed by subtracting the overall
163 mean (across all three populations) of all subjects from each individual's score and dividing it by
164 the overall standard deviation in order to equalize the scale across measures, and facilitate data
165 visualization and statistical analysis. Z-scores for the ADAS-Cog, GDS, and TMT were inverted
166 so that in all measures, higher scores reflect better performance. To investigate the relationship
167 between the EEG Spectral Power Ratio and cognitive function, three composite scores were
168 computed by averaging together Z-scores of tests that tap into similar cognitive processes or
169 measures: *Dementia severity* (ADAS-Cog, ADLs; measuring general cognitive functioning and
170 functional independence), *Executive functions* (Digit Span forward and backward, TMT_{B-A}
171 Semantic fluency, DSST; measuring attention, working memory, set-shifting, strategic thinking
172 and psychomotor processing speed); and *Learning and memory* (RAVLT, Logical Memory;
173 measuring the acute ability to learn and recall verbal information with and without context). This
174 approach—modelled after one from the Alzheimer's Disease Neuroimaging Initiative (Crane et
175 al., 2012; Gibbons et al., 2012) and used in a prior neuroimaging study (Buss et al., 2018)—
176 allowed oscillatory activity to be related to broad categories of cognitive processing rather than
177 to specific tests.
178
179 *Electroencephalography acquisition and preprocessing*
180 Resting-state EEG was recorded using a 64-channel system (eXimia EEG, version 3.2, Nexstim
181 Ltd, Finland) with a sampling rate of 1450Hz. EEG was acquired using an extended version of
182 the "International 10-20 system" (**Supplementary Figure S1**). Ground and reference electrodes
183 were placed on the forehead and two additional electrooculography electrodes (EOG) were

placed below and at the outer canthi of the left eye to identify vertical and horizontal eye movements. Impedances for all electrodes were kept below 5 kΩ. A 5-minute resting-state EEG recording was obtained while subjects sat in a semi-reclined armchair with their eyes closed. During recordings, the participants were instructed to remain quiet with their face muscles relaxed. The participant and EEG were monitored for signs of drowsiness at which point the participant was asked to blink their eyes a few times before closing them again. EEG data preprocessing was performed offline using a combination of the EEGLab toolbox (Delorme and Makeig, 2004a) and custom scripts in Matlab 2016a (Mathworks, USA). Data were filtered for line noise using a 55-65 Hz notch filter. Additional low-pass (100 Hz) and high-pass (1 Hz) filters were applied using a zero-phase second-order Butterworth filter. Filtered recordings were divided into 3-second epochs for visualization. Faulty or excessively noisy channels were visually detected and removed (average ±SD channels removed = 3.9 ±2.3; range = 0-9) and the remaining data were re-referenced to the average of all channels. After re-referencing, noisy epochs were identified semi-automatically and those containing excessive artifacts were rejected after visual inspection (average ±SD epochs removed = 25.9 ±20.5; range = 2-88), resulting in 48-116 usable epochs per participant with an average (±SD) of 86.9 (±14.0). Independent components analysis (ICA) was performed on cleaned data using fastICA (Rogasch et al., 2014), and components corresponding to blink/oculomotor, muscle or transient electrode artifacts were subtracted from the data. After component rejection, previously rejected channels were interpolated using a spherical spline interpolation and the data were down-sampled to 1024Hz.

Experimental design and Statistical Analysis

Electroencephalography

After EEG preprocessing, mean absolute power spectral density across epochs was calculated for each frequency band (1-40 Hz, 0.5 Hz resolution) at all electrodes using the *spectopo*

EEGlab function (window-size = 1024 samples, window-overlap = 512 samples) (Delorme and Makeig, 2004b). The power estimates for each frequency band were further divided by the sum of estimates across all frequencies in order to calculate the relative power of each frequency within the spectrum. To investigate group differences in EEG power, an analysis of covariance (ANCOVA) was performed at all electrode-frequency (1:40 Hz) points. The ANCOVA model included *EEG power* as the outcome measure, *Diagnosis* (HC, T2DM, AD) as a grouping variable, and *Age* as a continuous predictor to control for its effects on group differences in EEG power. Follow-up pairwise contrasts between groups were calculated using the Tukey-Kramer method. To control for the large number of multiple comparisons across electrode-frequency space, a non-parametric cluster based permutation approach was adopted (Maris and Oostenveld, 2007). Calculation of the test statistics involved the following: based on the initial ANCOVA's and follow-up contrasts performed at all electrode-frequency points, data points corresponding to an uncorrected p-value < 0.05 were formed into clusters by grouping together adjacent significant electrode-frequency points. Note that for a sample to be included in a cluster it was required to have at least 1 neighboring significant sample in either frequency or space. The spatial neighborhood of each electrode was defined as all electrodes within 4 cm, resulting in a mean of 2.9 (min = 1, max = 4) and median of 3 neighbors per electrode. The *F*-values (overall ANCOVA) or t-values (follow-up contrasts) within each identified cluster were summed to produce a cluster-level statistic. For the follow-up contrasts, the cluster-building procedure was performed separately for data points with positive and negative *t*-values (two-tailed test). Subsequently, this cluster-building procedure was repeated across 2000 permutations of the data. On each iteration, diagnostic group labels were randomly shuffled, thereby cutting the hypothesized relationship between diagnostic group and EEG power. The most extreme cluster-level *F*- or *t*-score was retrieved on each iteration to build data-driven null hypothesis distributions, separately for both the overall model and for each of the follow-up contrasts. The location of an original real cluster statistic within the null hypothesis distribution

indicates how probable such an observation would be if the null hypothesis were true (*F*-test: No difference in EEG power between any of the groups. Follow-up *t*-tests: No difference in EEG power between given two groups). For the overall model, if a given real cluster had a cluster-statistic > 95% of the respective null distribution cluster-statistics, then this was considered a significant effect (5% α level). For the follow-up contrasts, if a given negative/positive cluster had a cluster-statistic lower/higher than 97.5% (2.5% α per tail) of the respective null distribution cluster-statistics, then this was considered a significant effect (5% total α level). This entire analysis was performed separately for both absolute and relative EEG power.

EEG frequency bands and *Spectral power ratio*

For subsequent analyses of EEG power, including its relationship with cognitive function, relative and absolute power estimates were extracted for each classical frequency band: δ (1-4 Hz), θ (4-8 Hz), α (8-13 Hz), β (13-30 Hz), and gamma (γ; 30-40 Hz). Absolute power estimates were used to compute the *Spectral Power Ratio*, defined as the ratio of power in α and β to power in δ and θ: (α+β)/(δ+θ) (**Supplementary Table S2**). This approach has been utilized to assess alterations in the frequency distribution of EEG power, capturing in a single variable the pattern of a general shift in power from higher to lower frequencies that has been previously reported in AD (Babiloni et al., 2004; Bennys et al., 2001; Brenner et al., 1986; Coben et al., 1983; Moretti et al., 2004). In order to assess the spatial distribution of the effects, the average of the relative power estimates for each frequency band and the average of the *Spectral power ratio* values were calculated separately for four cortical regions of interest (ROIs): *Frontal* (incorporating electrodes FP1, FPz, FP2, AF1, AFz, AF2, F5, F1, Fz, F2, F6), *Central* (FC5, FC3, FC1, FCz, FC2, FC4, FC6, C5, C3, C1, Cz, C2, C4, C6, CP5, CP3, CP1, CPz, CP2, CP4, CP6), *Temporal* (F7, F8, FT9, FT7, FT8, FT10, T3, T4, TP9, TP7, TP8, TP10), and *Posterior* (P9, P7, P3, P1, Pz, P2, P4, P8, P10, PO3, POz, PO4, O1, Oz, O2, Iz).

The relative power estimates from each of the four frequency bands plus the *Spectral power ratio* values were assessed independently via five mixed-effects linear regression analyses, each with a full-factorial model comprised of the between-subjects factor *Group* and the within-subject factor *Cortical ROI* (crossed with the random factor *Subject* to control for variance associated with repeated observations within the same individual), plus *Age* as a covariate (for details on the linear regression analysis of *Spectral power ratio* in the age-matched subgroup cohort, see Supplementary materials). Each of the five analyses was followed by four fixed-effect linear regression analyses to test for group differences within each ROI separately. Significance values for these 20 follow-up analyses were adjusted for multiple comparisons using Holm-Bonferroni correction. Finally, post-hoc Tukey's HSD tests were used to test for pairwise differences between groups.

Analysis of neuropsychological performance and its relationships with *Spectral power ratio*

Multivariate analyses of variance (MANOVAs) with a Wilk's lambda (λ) distribution were used to compare neuropsychological performance across groups (MANOVA-1) and investigate its relationship with the *Spectral power ratio* across ROIs (MANOVA-2).

MANOVA-1 was performed on Z-scores for the individual neuropsychological tests with the main factor of *Group* (HC, T2DM, AD), and *Age* as a covariate (for details on the MANOVA-1 in the age-matched subgroup cohort, see Supplementary materials). Follow-up analyses consisted of separate linear regression models for each cognitive measure. Tukey's HSD pairwise comparisons were performed for any regression model that survived a 5% false discovery rate (FDR) correction (Benjamini and Yekutieli, 2001).

To investigate relationships between the *Spectral power ratio* and cognitive functions, MANOVA-2 was performed on the three composite scores with the factors *Group*, *Cortical ROI* and *Spectral power ratio* in a full-factorial model, plus *Age* as a covariate. Follow-up linear

regression analyses were performed for each domain (*Learning and memory*, *Dementia severity*, *Executive functions*), with the factors *Group* and *Spectral power ratio* in a full-factorial model with *Age* as a covariate (for details on the MANOVA-2 in the age-matched subgroup cohort, see Supplementary materials). As all effects that included the factor *Cortical ROI* were highly non-significant (see **Results**), it was excluded from post-hoc analyses. For *Learning and memory*, the *Group*Spectral power ratio* interaction was highly non-significant (see **Results**), so the model was rerun without that term. From these models, an overall correlation coefficient was calculated to express the relationship between the composite score and *Spectral power ratio* across all participants. Lastly, simple linear regression analyses were performed to assess the association of *Spectral power ratio* with each composite cognitive score in each group. Individual *p*-values for these 9 group-specific post-hoc analyses were adjusted for multiple comparisons with a 5% FDR.

Individual α and posterior dominant frequencies

During eyes-closed wakefulness, one of the most prominent features of the EEG signal is α-band (~8-13Hz) activity, leading to the characteristic α peak in the power spectrum (Klimesch, 2012; Keitel et al., 2019). We sought to investigate group differences in this dominant frequency, and whether these differences were related to cognitive function, using two independent metrics. First, in each participant we identified the individual frequency between 5-15 Hz with the highest power density across all posterior electrodes using an automated peak-finding algorithm based on smoothing of the 2nd order gradient of power spectral density (PSD) estimates with an 11-point, 3rd order polynomial Savitzky-Golay filter (Savitzky and Golay, 1964; Corcoran et al., 2018; Keitel et al., 2018; Benwell et al., 2019). The posterior electrodes included in the analysis were P9, P7, P3, P1, Pz, P2, P4, P8, P10, PO3, POz, PO4, O1, Oz, O2 and Iz**.** This approach incorporated a wider band of activity than the typical α range in order to capture potentially large shifts in the dominant frequency. Hence, we labelled this the *Dominant*

frequency analysis. In parallel, to look specifically at frequency and power changes within the classic α-range (8-12 Hz), two clinical neurophysiologists trained to interpret EEG (authors PDP and MMS) manually estimated the *individual α frequency (IAF)* for each participant using visibly-identifiable alpha activity from the occipital and parieto-occipital electrodes. We labelled this the *IAF* analysis. For both the *Dominant frequency* and *IAF* analyses, we obtained both the peak frequency itself and the power density value averaged over the peak frequency ± 2.5 Hz. Hence, we were able to test simultaneously for group differences in both the peak frequency itself and the surrounding power density. These metrics were each entered into separate one-way ANOVAs (with *Age* as a covariate) to investigate group differences and were also correlated with the cognitive composite scores.

Results

Participant characteristics

By design, MMSE scores were lower in the AD group relative to both T2DM and HC. AD participants were also significantly older than HC, but not T2DM. The groups were equivalent in years of education, pre-morbid IQ, and proportions of men and women (for full details on participant characteristics across groups, see **Supplementary Table S1**).

EEG Power

The following details the results of the primary analysis of relative EEG power. For equivalent analyses of absolute EEG power and their results, see Supplementary Materials Section 1 (including **Table S2** and **Figure S2**).

A main effect of *Group*, controlling for *age*, was identified in the δ+θ frequency bands (~1–7 Hz) and also in the α+β (~8.5–21 Hz) and low–γ bands (30–40 Hz, **Figure 1A-B**). Relative δ+θ power were higher for AD compared to T2DM and HC, whereas relative α+β power were lower

for AD compared to T2DM and HC (**Figure 1C**). Pairwise contrasts (**Figure 1D-F**) demonstrated higher relative δ+θ power in AD than both HC and T2DM, and lower relative α+β power in AD compared to either HC or T2DM. Additionally, there was significantly higher relative power in the low–γ band in AD compared to HC. No clusters survived correction for the T2DM-HC contrast.

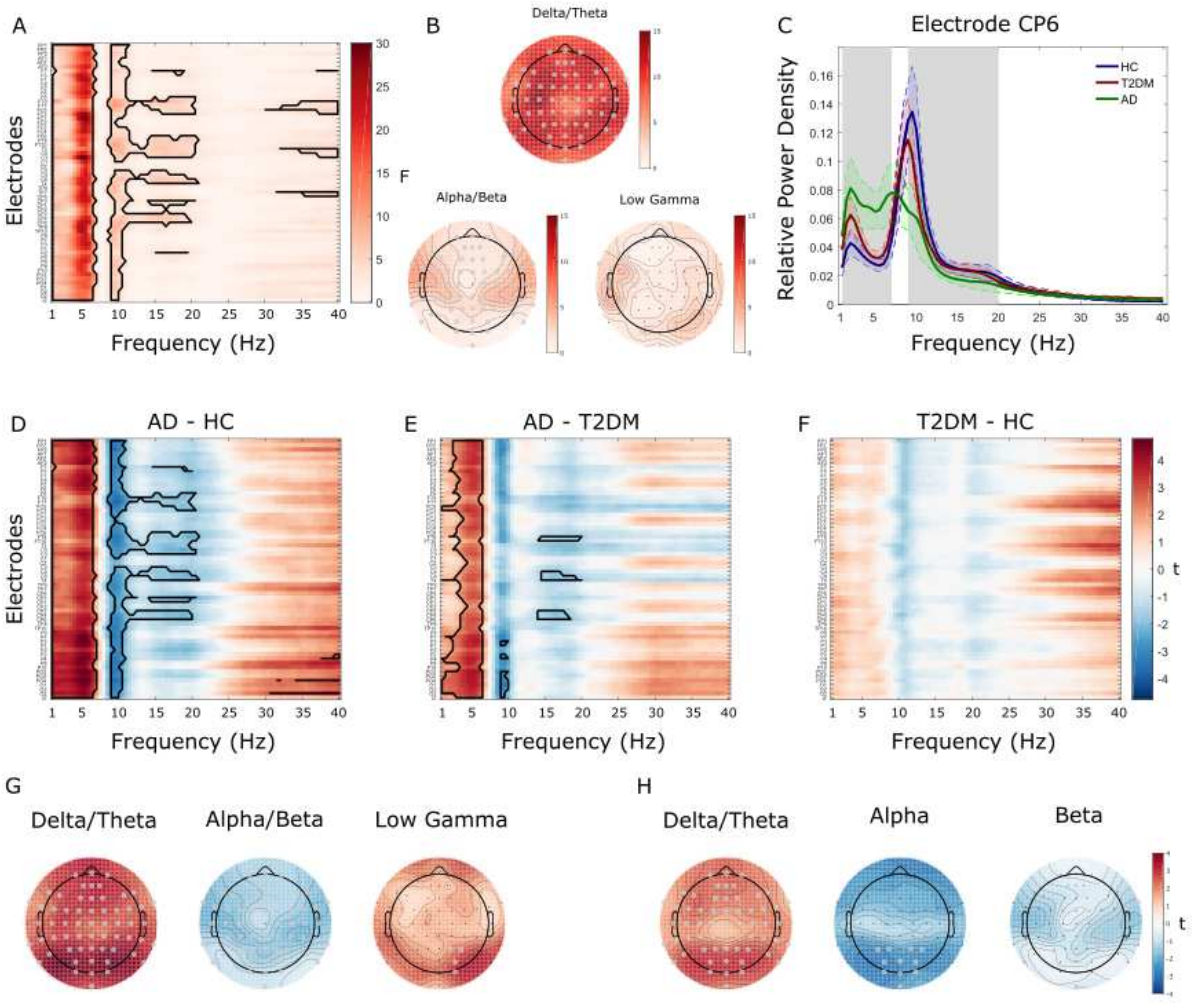

Figure 1. *Whole-brain analysis of relative power.* **A.** *F*-ratios associated with between-group mass univariate analyses of variance (ANOVAs) comparing relative electroencephalography (EEG) power between Alzheimer's disease (AD), Type-2 diabetes mellitus (T2DM), and healthy controls (HC) across all electrodes (y-axis) and frequencies (x-axis). The solid black contour represents data points surviving cluster-based multiple comparison correction. **B.** Topographic representation of the *F*-ratios averaged across the significant frequencies. **C.** Mean power spectra (with 95% confidence intervals) for each group separately at the electrode (CP6) for which group differences were maximal. Alpha/beta power showed a linear decrease across groups, being highest for HC and lowest for AD with T2DM having intermediate values whereas delta/theta power showed a linear increase across groups. **D-F**. *T*-values associated with follow-up tests comparing relative EEG power between each pair of groups separately. Solid

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black contours indicate data points surviving cluster-correction. **G-H**. Topographic representation of the *t*-values associated with the respective significant effects. Significant electrodes are highlighted in gray.

Classic EEG frequency bands across ROIs

Delta: There were significant main effects of *Group* ($F_{2,68}$ = 8.7, p < .001) and *Cortical ROI* ($F_{3,207}$ = 59.1, p < .001), but no *Group*Cortical ROI* interaction ($F_{6,207}$ = 1.2, p = .292). Follow-up tests showed a similar pattern of group differences across the four Cortical ROIs (p values < .015, adjusted), with AD showing greater relative δ power than both HC and T2DM (p values < .05).

Theta: There were significant main effects of *Group* ($F_{2,68}$ = 12.7, p < .001) and *Cortical ROI* ($F_{3,207}$ = 3.3, p = .023), but no *Group*Cortical ROI* interaction ($F_{6,207}$ = 2.1, p = .060). Follow-up tests showed a similar pattern of group differences across the four ROIs (p values < .004, adjusted), with AD showing greater relative θ power than both HC and T2DM (p values < .05).

Alpha: There were significant main effects of *Group* ($F_{2,68}$ = 9.9, p < .001) and *Cortical ROI* ($F_{3,207}$ = 61.7, p < .001), as well as a *Group*Cortical ROI* interaction ($F_{6,207}$ = 4.9, p < .001). Follow-up tests showed somewhat different pattern of group differences across the four ROIs (p values < .013, adjusted). Relative α power was lower in AD than HC across all ROIs. Relative α power was also lower in AD than in T2DM in the *Frontal*, *Temporal*, and *Posterior* (but not *Central*) ROIs. T2DM had significantly lower α power than HC in the *Temporal* ROI only (all p values < .05).

Beta: There was a significant main effect of *Cortical ROI* ($F_{3,207}$ = 47.5, p < .001), while *Group* ($F_{2,68}$ = 1.1, p = .337) and *Group*Cortical ROI* were not significant ($F_{6,207}$ = 1.8, p = .094). Follow-up tests showed a similar pattern of equivalent β power across groups, regardless of the ROI (p values > .7, adjusted).

Spectral power ratio: There were significant main effects of *Group* ($F_{2,68}$ = 9.2, p < .001) and *Cortical ROI* ($F_{3,207}$ = 20.8, p < .001), as well as a *Group*Cortical ROI* interaction ($F_{6,207}$ = 3.3, p = .004). Follow-up analyses showed a pattern of group differences in *Posterior* ROI (HC > AD; p = .012, adjusted) that was distinct from the other ROIs (HC, T2DM > AD; p values < .008, adjusted) (**Figure 2**). These results indicate a shift of power from higher frequencies to lower frequencies in AD and suggest a similar pattern may be emerging in T2DM. Of note, an equivalent analysis in the age-matched sub-cohort demonstrated essentially identical findings (see Supplementary materials Section 2).

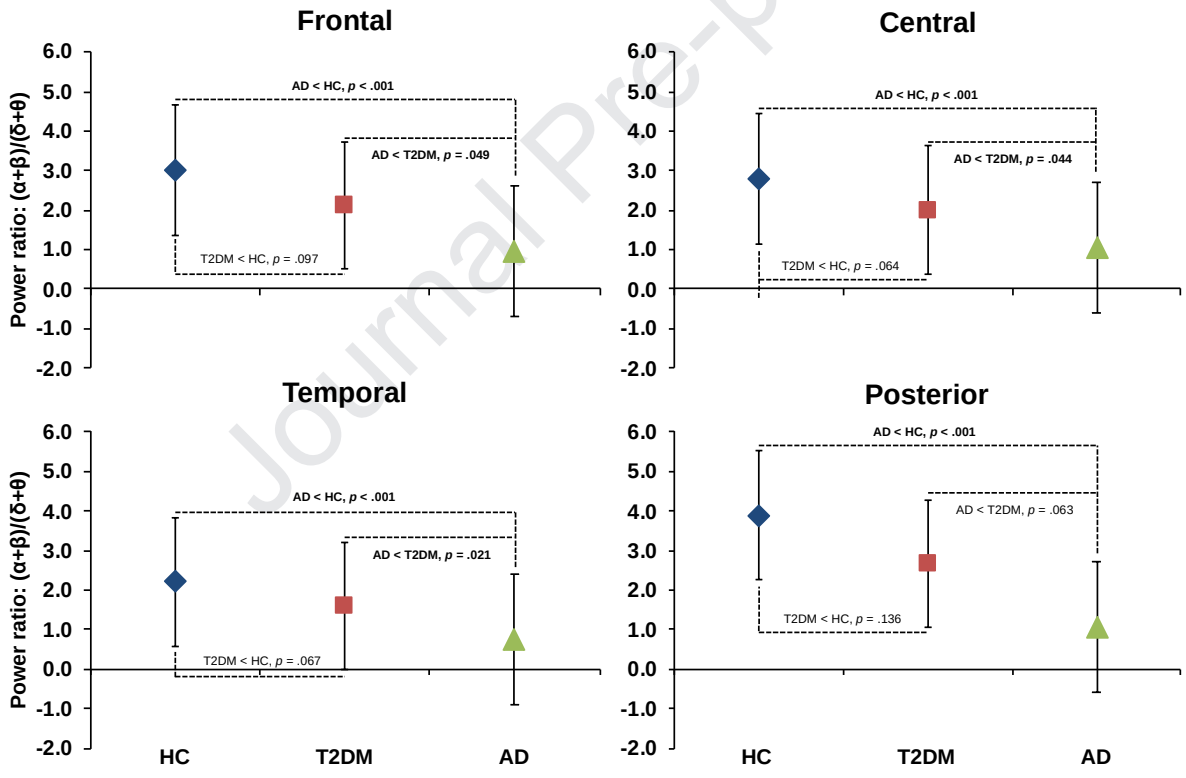

Figure 2. *Spectral power ratio.* Figure shows the age-adjusted comparison across groups of the Spectral Power Ratio (α+β)/(δ+θ) estimated from each cortical region of interest (ROI). Tukey's Honestly Significant Difference post-hoc tests demonstrated that (α+β)/(δ+θ) was lower in Alzheimer's disease (AD) than in Healthy Controls (HC) across all ROIs (p values < 0.001) and lower than Type-2 Diabetes (T2DM) in all but the *Posterior* ROI (p values = 0.0499 – 0.063). T2DM was lower than HC across all ROIs though this difference did not reach significance (p *values* = 0.064 – 0.136). Data shown represent the least squared means and standard deviations derived from the linear regression models.

Neuropsychological function and relationship to EEG spectral power

Group averaged neuropsychological test scores (z-scored) are displayed in **Figure 3**.

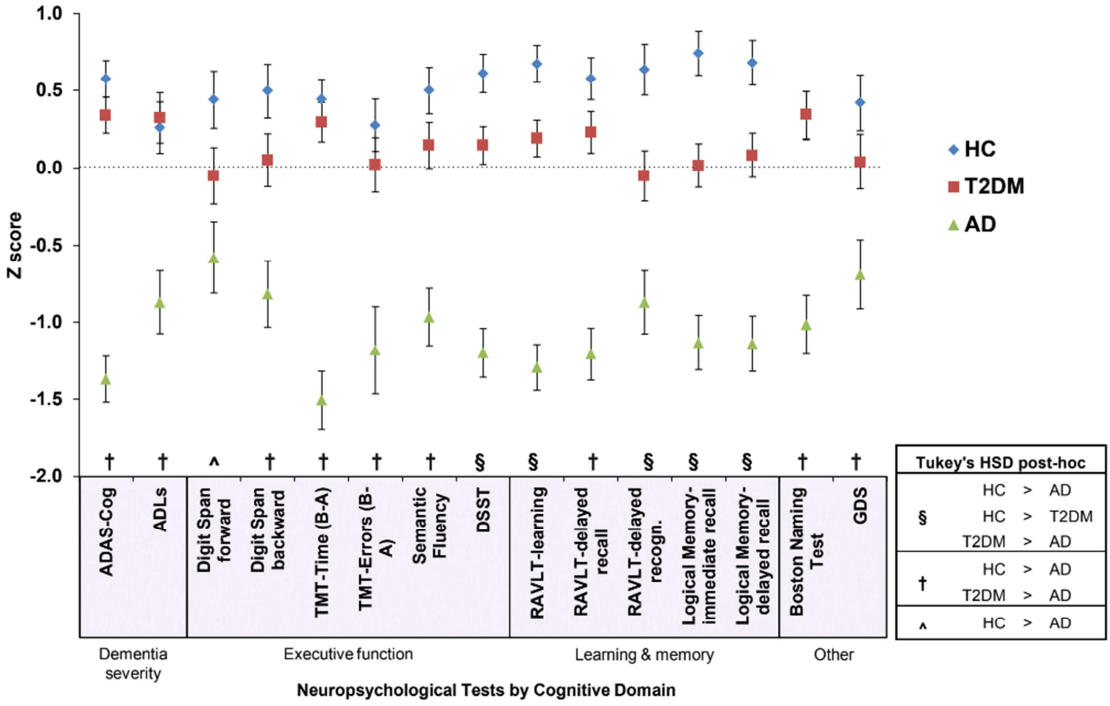

Figure 3. *Group analysis and post-hoc comparisons of cognitive measures adjusted for age.* All data represent least squared means and standard error. Individual neuropsychological tests (x-axis) are shown grouped by cognitive domain. Scores (y-axis) were z-normalized and inverted (if necessary) so higher numbers reflect better performance/function. Following the first omnibus multivariate analysis of variance (MANOVA-1), group performance on individual tests was assessed using separate multiple linear regression analyses with age as a covariate. All results survived a 5% false discovery rate (FDR). In general there was a continuum of deficits with healthy controls (HC) scoring higher than Type-2 diabetics (T2DM), who performed better than Alzheimer's disease (AD). Post-hoc pairwise comparisons were conducted with Tukey's honestly significant difference (HSD) tests. Three patterns were observed: (§) all three groups were significantly different; (†) AD scored significantly worse than both HC and T2DM, which were equivalent to each other; (^) HC were significantly better than AD, with T2DM not significantly different from either group. *Additional abbreviations*. Alzheimer's disease Assessment Scale-Cognitive subscale (ADAS-Cog); Activities of Daily Living (ADLs); Digit Symbol Substitution Test (DSST); Trail Making Test (TMT); Rey Auditory Verbal Learning Test (RAVLT); Geriatric Depression Scale (GDS).

MANOVA-1 (**Table 1**) demonstrated that the variance in cognitive scores was different between the groups after controlling for *Age*, $F_{(30,\ 86)}$=6.7, η^2_p=0.70, p<0.001, while *Age* itself was not a predictor of cognitive function, $F_{(15,43)}$=1.7, η^2_p=0.37, p=0.096. Follow-up linear regression analyses yielded significant variance by *Group* for each neuropsychological measure

after controlling for *Age* (*F*'s>5.7, *p*'s<0.006: see **Supplementary Table S3**). All measures survived a 5% FDR correction. For equivalent analyses in the age-matched sub-cohort with similar findings, see Supplementary materials Section 2.

Table 1. *Results of Multivariate Analyses of Variance (MANOVAs).*

MANOVA-1

Factor	Wilks' λ	*df*	*F* ratio	*P* value	Partial Eta^2
Group	0.090	30,86	**6.670**	**<.001**	**0.699**
Age	0.581	15,43	1.666	0.0958	0.368

MANOVA-2

Factor	Wilks' λ	*df*	*F* ratio	*P* value	Partial Eta^2
Group	0.550	6,522	**30.200**	**<.001**	**0.260**
Spectral Power Ratio	0.399	3,261	**36.100**	**<.001**	**0.290**
*Group*Spectral Power Ratio*	0.532	6,522	**29.100**	**<.001**	**0.250**
Age	0.215	3,261	**6.200**	**<.001**	**0.070**

In MANOVA-1, the dependent variables included z-normalized, rectified scores on the Alzheimer's disease Assessment Scale-Cognitive Subscale, Activities of Daily Living, Digit Symbol Substitution Test, Semantic Fluency Test, Trail Making Test time and errors (difference Part B-Part A), Digit Span length forward and backward, Rey Auditory Verbal Learning Test (learning, delayed recall, delayed recognition), Logical Memory story (immediate and delayed recall), Boston Naming Test, and Geriatric Depression Scale. In MANOVA-2, the dependent variables include the averaged Z-scores of the three cognitive domains (Learning & memory, Dementia severity, Executive function). Spectral Power Ratio refers to a whole-brain averaged power ratio [(alpha + beta)/(delta + theta)] obtained from eyes-closed resting-state electroencephalography.

Following Tukey's HSD comparisons, two major patterns emerged (**Figure 3**): For scores on the DSST, RAVLT learning and delayed recognition trials, Logical Memory immediate and delayed recall trials, there were significant differences between all three groups with AD < T2DM < HC (*p*'s<0.03). By comparison, on the ADAS-Cog, ADLs, Semantic fluency, TMT time, TMT errors, Digit Span backward, RAVLT delayed recall, Boston Naming Test, and GDS, the AD group performed worse than either the HC or T2DM groups (*p*'s<0.04), while the latter two groups did not differ from each other (*p*'s>0.2). Lastly, on the Digit Span forward test was there a difference only between HC and AD (*p*=0.004) with T2DM not different from either HC or AD (*p*>0.1).

Concerning the association of cognitive function with the *Spectral power ratio*, MANOVA-2 (**Table 1**) indicated a main effect of *Group*, Wilks' λ=0.55, $F_{(6,522)}$=30.2, η^2_p=0.26, p<0.001, and an overall relationship between the composite neuropsychological scores and the *Spectral power ratio*, $F_{(3,261)}$=36.1, η^2_p=0.29, p<0.001. In addition, there was a *Group*Spectral power ratio* interaction, $F_{(6,522)}$=29.1, η^2_p=0.25, p<0.001, indicating that the overall relationship between cognition function and (α+β)/(δ+θ) differed between groups. Importantly, none of the effects that included *Cortical ROI* as a factor were significant (*F* ratios < .7, *p* values > .78), indicating that the overall relationship between the (α+β)/(δ+θ) and cognitive function did not vary as a function of cortical region. In contrast to MANOVA-1, *Age* was a predictor of cognitive function after controlling for *Group, Cortical ROI,* and *Spectral power ratio*, $F_{(3,261)}$=6.2, p<.001. Post-hoc linear regression analyses showed that across all participants, *Spectral power ratio* had significant positive associations with *Learning and memory* (R_{67}=0.27, p=0.040), *Dementia severity* (R_{65}=0.44, p<0.001), and *Executive functions* (R_{65}=0.43, p<0.001) (**Figure 4**); partial correlation coefficients were calculated from a model that included *Group*, *Age*, and the *Group*Spectral power ratio* interaction (except *Learning and memory*, for which the interaction term was highly non-significant, p=0.954).

Considering cognition-EEG relationships within each group separately, higher *Spectral power ratio* was associated with better *Learning and memory* performance in HC (**Figure 4A**; p=0.018, uncorrected). In AD, higher (α+β)/(δ+θ) was associated with lower *Dementia severity* (**Figure 4B**) and better *Executive function* performance (**Figure 4C**), *p's*<0.05, uncorrected). In contrast to HC and AD, no significant relationships were observed for T2DM (*p*'s>0.1). After subjecting *p*-values to a 5% FDR, the relationship between *Spectral power ratio* and *Executive function* in AD remained significant (*p*'s<0.05).

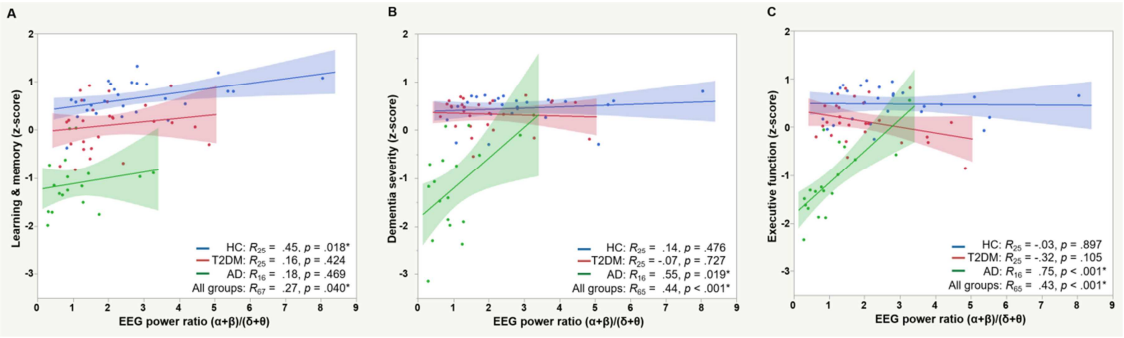

Figure 4. *Relationship between electroencephalography (EEG) Spectral Power Ratio and cognitive function.* Z-normalized scores (higher score indicates better performance) from individual neuropsychological tests were averaged together to form three domains: **A.** *Learning & memory* (Rey Auditory Verbal Learning Test, Logical Memory Story); **B.** *Dementia severity* (Alzheimer's disease Assessment Scale-Cognitive subscale, Activities of Daily Living); **C.** *Executive function* (Digit Symbol Substitution Test, Semantic fluency, Trail Making, Digit Span forward and backward). Computed averages were related to the EEG Spectral Power Ratio (α+β)/(δ+θ) and plotted separately for the three groups. In healthy controls (HC), higher (α+β)/(δ+θ) was significantly associated with better *Learning & memory* performance (p = 0.018, uncorrected). In Alzheimer's disease (AD), higher (α+β)/(δ+θ) was significantly associated with better *Dementia severity* and *Executive function* (p's < 0.05, uncorrected). By contrast, no significant relationships were observed in the Type-2 diabetes mellitus (T2DM) group (p's > 0.1).

Individual alpha and posterior dominant frequencies

Dominant frequency (see **Figure 5A**): A main effect of *Group*, controlling for *Age*, was identified ($F_{(2,68)}$ = 6.26, η^2_p = 0.22, p = 0.001). The *Dominant frequency* was significantly lower in AD (mean = 8.2 Hz) compared to both T2DM (9.4 Hz: p = 0.002) and HC (9.3 Hz: p = 0.003). There was no significant difference between T2DM and HC (p = 0.99).

Power density at dominant frequency (see **Figure 5B**): A main effect of *Group* was identified ($F_{(2,68)}$ = 3.41, η^2_p = 0.09, p = 0.039). Power density in the *Dominant frequency* band was significantly lower in AD compared to HC (p = 0.05) but not compared to T2DM (p = 0.47). There was no significant difference between T2DM and HC (p = 0.08).

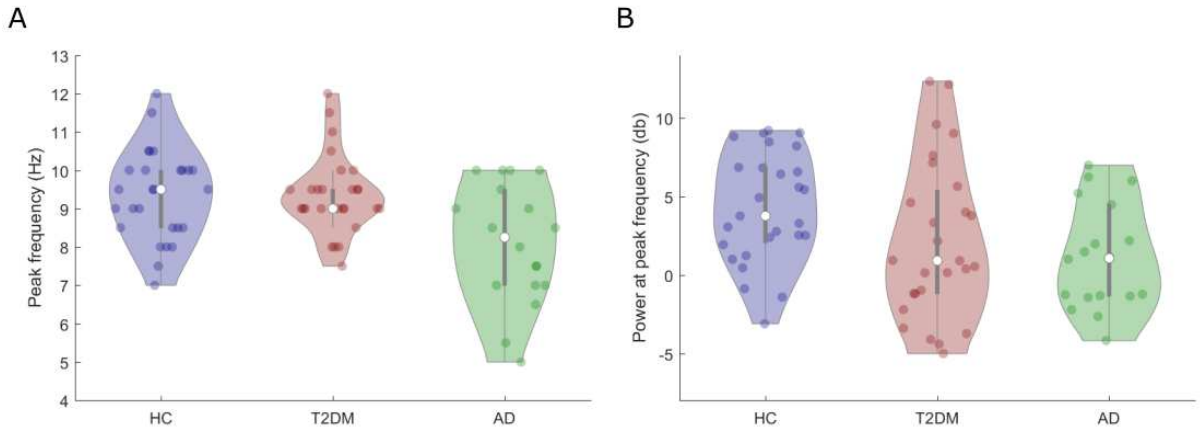

Figure 5. Group analysis of posterior dominant frequencies. **A**. Individual frequency between 5-15 Hz with the highest power density across all posterior electrodes (posterior dominant frequency) as a function of group (Healthy controls (HC), Type-2 diabetes mellitus (T2DM) and Alzheimer's disease (AD)). **B.** Power density at the posterior dominant frequency (averaged over the peak frequency ± 2 Hz) as a function of group. Colored dots denote individual participants, white dots denote group medians and background fills represent kernel density estimates.

Similar results were found for the *IAF* analysis (see supplementary Section 3 and Figure S3). Hence, there was a shift of the dominant rhythm towards lower frequencies in AD relative to both T2DM and healthy controls. However there is also a reduction in power at both the *Dominant frequency* and the *IAF* in AD. Intriguingly, T2DM showed significantly higher *Dominant frequency* and *IAF* values compared to AD (in line with HC), but did not show any significant difference in terms of power density at either the *Dominant frequency* or the *IAF* (in contrast to HC). This suggests that, unlike in AD, the frequency of the dominant posterior rhythm in T2DM is indistinguishable to that observed in HC. However, in terms of power density at the dominant rhythm, T2DM resembled AD more closely than HC.

In contrast to the *Spectral power ratio,* there was no significant relationship between any of the composite cognitive measures and either the Dominant Frequency or IAF.

Discussion

The present study compared oscillatory power and neuropsychological function (and their relationship) between HC, AD and T2DM in order to better understand pathophysiological

signatures of cognitive aging. Cognitively, AD was associated with deficits across almost all neuropsychological tests, whereas T2DM was associated with selective deficits in verbal/episodic learning, memory and psychomotor processing speed. Neurophysiologically, there was a pattern of shifting EEG power from higher to lower frequencies in AD, and evidence that a similar shift is also apparent to a lesser degree in T2DM, particularly over temporal regions. Capturing this shift as a single measure (the ratio of α+β/δ+θ power) across participants allowed us to investigate the relevance of these oscillatory changes for cognitive aging. This *Spectral power ratio* was uniquely associated with executive functions and dementia severity in the AD group, and with learning and memory function in the HC group. The results suggest that a shift in EEG power from higher to lower frequencies represents a candidate biomarker for specific cognitive deficits associated with aging and brain-related diseases.

Some of the results replicate findings from previous studies which, particularly given recent concerns about the reproducibility of scientific findings in both neuroimaging (Poldrack et al., 2017) and psychology (Open Science Collaboration, 2015), is of great importance in establishing the reliability of the reported effects. Moreover, the current findings go beyond replication to extend prior work by collapsing the spectral power distribution into a single easily obtainable summary metric, and then examining how this metric relates to specific domains of cognitive function. We contribute several important novel insights into the pathophysiology of cerebral oscillations in AD and T2DM relative to normal cognitive aging. The novel aspects include (1) a direct comparison of EEG activity and neuropsychological performance between AD, T2DM and healthy controls, (2) extensive testing of group differences in both absolute and relative EEG power across all electrodes and a wide range of frequencies (1-40 Hz), (3) a parsing of the relationship between oscillatory abnormalities and specific cognitive domains (i.e. memory versus executive function) across the different groups, (4) evaluation of the distribution

of frequency changes across different brain regions, and (5) analyses of shifts in the *Dominant frequency*, as well as in the power density at this individually-defined dominant frequency.

Differences in cognitive function associated with AD and T2DM

AD participants showed marked neuropsychological deficits relative to both HC and T2DM. The most prominent deficits were observed on learning, memory and executive function tests. AD participants also reported impaired function in activities of daily living and increased symptoms of depression compared to both HC and T2DM. These symptoms are well established in AD (Burns and Iliffe, 2009).

Additionally, a pattern of performance differences was observed from HC to T2DM to AD on verbal/episodic learning (RAVLT and Logical Memory) and psychomotor processing speed (DSST). These findings accord with previous reports of mild decrements in memory, motor function and attention and perceptual processing speed in T2DM relative to HC (Cheng et al., 2012; Marseglia et al., 2016; Mooradian et al., 1988; Palta et al., 2014; Takeuchi et al., 2012; van den Berg et al., 2010). Thus, T2DM may affect these cognitive domains first, and the effects are detectable using commonly employed neuropsychological tests. It is important to acknowledge that cognitive impairment in T2DM is likely modulated by many variables, including vascular risk factors (Marseglia et al., 2016), presence of the apolipoprotein ε4 allele (Ravona-Springer et al., 2014) and glycemic control (Yaffe et al., 2012). These factors were not controlled for here, and may have contributed to the observed cognitive deficits. However, the current results provide evidence that mild neuropsychological deficits are detectable in T2DM even when participants report no cognitive impairment.

Changes in oscillatory activity and relationship with cognition in AD

The present study suggests that both AD and T2DM are associated with abnormal neural oscillations, relative to HC. In AD, we observed reduction in α+β power and increase in δ+θ

power, in line with previous findings (Babiloni et al., 2016; Bennys et al., 2001; Brenner et al., 1986; Coben et al., 1990, 1983; Dierks et al., 1995; Fraga et al., 2013; Jeong, 2004; Moretti et al., 2004; Neto et al., 2016). There was a similar pattern of higher δ+θ power (HC < AD), and a similar pattern of lower α+β power (HC > AD), across all ROIs. These oscillatory signatures, as captured by the ratio of (α+β)/(δ+θ) power, correlated with learning and memory function across all groups combined, though the correlation was relatively weak within each group and only significant in HC. In AD, the *Spectral power ratio* was strongly associated with executive function performance and dementia severity, with the degree of change being positively correlated with symptom severity. Previous studies have found a correlation between band-specific EEG power and the severity of cognitive deficits in AD (Babiloni et al., 2007, 2006a; Dierks et al., 1995; Helkala et al., 1991; Luckhaus et al., 2008; Moretti et al., 2009; van der Hiele et al., 2007). The current results confirm and expand on this literature, suggesting that the ratio of (α+β)/(δ+θ) power is a strong predictor specifically of executive function in AD (accounting for more than 55% of the variance). Notably, the *Spectral power ratio* was also associated with overall dementia severity, suggesting that deficits in executive functions (as opposed to learning and memory) may be more closely tied to global indicators of dementia. Intriguingly, similar neural changes are predictive of progression from MCI to dementia (Babiloni et al., 2011; Grunwald et al., 2001; Jelic et al., 2000, 1996; Rossini et al., 2006) and have been associated with cognitive deficits in disorders such as ADHD (Barry et al., 2003), dyslexia (Penolazzi et al., 2008), schizophrenia (Bates et al., 2009; Boutros et al., 2008) and Parkinson's disease (Klassen et al., 2011; Olde Dubbelink et al., 2014).

In line with previous studies (Moretti et al., 2004; Poza et al., 2007; Babiloni et al., 2015), we found lower dominant posterior frequencies in AD (mean = 8.2 Hz) relative to both HC and T2DM, who showed typical mean dominant frequencies in the α-band (Klimesch, 1999; Mierau et al., 2017; Knyazeva et al., 2018). However, in contrast to the *Spectral power ratio*, we found no relationship between the posterior *dominant frequency* or IAF and performance on any of the

590 composite cognitive scores. This suggests that pathophysiological changes in power density in
591 AD are more cognitively relevant than changes in peak frequency.
592
593 *Changes in oscillatory activity and relationship with cognition in T2DM*
594 Interestingly, α+β power density in T2DM participants was intermediate between HC and AD
595 participants. This finding replicates and extends the results of Cooray et al. (2011), who found
596 that α+β power was reduced in T2DM compared to HC. We also found that T2DM is specifically
597 associated with a reduction of α power in the temporal regions, with no significant differences
598 observed in other brain regions relative to HC. This is notable insofar as deficits in temporal α
599 power have previously been linked to impairments in learning and memory in AD (Babiloni et al.,
600 2009). Interestingly, a subset of T2DM participants in the study of Cooray et al. (2011) who
601 received a 2-month glycemic control treatment showed an increase in α power, associated with
602 improvements in visuospatial and semantic memory performance. Collectively, these results
603 highlight alterations in brain function and α power associated with T2DM (Fried et al., 2017;
604 Strachan et al., 2011).
605 No difference was found between T2DM and HC in either the *Dominant posterior*
606 *frequency* or the *IAF*. However, despite the peak frequency remaining intact, a tendency was
607 observed for a reduction in power density at both the *Dominant posterior frequency* and the *IAF*,
608 with the power density profile in T2DM more closely resembling AD than HC. To our knowledge,
609 this represents the first analysis of peak frequencies in T2DM. Though we found no link
610 between these power density changes and neuropsychological performance in the current
611 sample, future longitudinal studies may investigate further whether they are cognitively relevant
612 and potentially prodromal of later changes in peak frequency.
613
614 *Differences in cognitive relevance of oscillatory signatures between AD and T2DM*

Though T2DM confers an increased risk for developing AD (Biessels and Kappelle, 2005; Barbagallo and Dominguez, 2014), little is known about the mechanistic underpinnings that link the two disorders (Chatterjee and Mudher, 2018; Chornenkyy et al., 2019). In contrast to AD, we found no correlation between the *Spectral Power Ratio* and the degree of cognitive impairment in T2DM for any of the neuropsychological tests in our battery. It is possible that this highlights the domain-specific nature of the EEG–cognition link, as the T2DM group showed no marked deficits on the executive function tests, which were most strongly related to the *Spectral Power Ratio* in AD. A related possibility concerns the multifactorial nature of T2DM-related impact on the brain. Despite some similarities in the observed EEG changes associated with AD and T2DM, the electrophysiological signatures linked to cognitive deficits may not be the same due to differing neurodegeneration and cerebrovascular pathologies. This proposal could be tested in future studies by combing resting-state EEG recordings and comprehensive neuropsychological testing with structural magnetic resonance imaging (MRI) in both AD and T2DM samples. This may allow for the establishment of a physiological link between oscillatory activity, structural abnormalities and cognitive functions. Such an approach would shed further light on similarities and differences in the neuropathological processes underlying cognitive impairment in T2DM and AD.

EEG oscillations and cognition

Oscillatory EEG activity reliably co-varies with cognitive functions in a band- and domain-specific manner (Basar et al., 2001). For example, α-band activity has been associated with memory (Bonnefond and Jensen, 2012; Klimesch, 1999; Palva and Palva, 2007), attention (Benwell et al., 2017, 2018; Foxe and Snyder, 2011), and arousal (Benwell et al., 2018; Cantero et al., 1999; Sadaghiani et al., 2010), while β-activity is believed to play a role in sensorimotor functions (Pfurtscheller et al., 1996) and the maintenance of top-down attention (Buschman and Miller, 2007; Engel and Fries, 2010). These findings have led to suggestions that oscillations are

641 computationally relevant for neuronal synchrony/communication and higher-order cognition
642 (Canolty and Knight, 2010).

643 Hence, changes in EEG power associated with pathophysiology may reflect abnormal
644 synchronization of large-scale networks of pyramidal cortical neurons and consequent
645 impairment of information transfer required for cognitive functions. Recent studies employing
646 both structural neuroimaging and EEG/MEG suggest that increases in δ+θ power (and
647 reductions in α power) correlate with neurodegenerative processes associated with AD such as
648 atrophy of sub-cortical white matter, cortical gray matter and hippocampus (Babiloni et al., 2013,
649 2006b; Fernandez et al., 2003; Helkala et al., 1996).

650 From a functional perspective, one theory linking frequency ratio changes with cognitive
651 impairment suggests a possible reciprocal relationship between α-band and low-frequency
652 (δ+θ) activity (Knyazev, 2012, 2007). Specifically, α-activity is implicated in controlling adaptive
653 functional inhibition (Klimesch et al., 2007), facilitating goal-directed sensory and behavioral
654 regulation. Accordingly, when this reciprocal relationship is unbalanced, through reductions in α-
655 mediated inhibition and/or abnormal increases in low-frequency activity, pathological
656 disinhibition occurs with consequent cognitive and behavioral impairments (Knyazev, 2012,
657 2007). Notably, differences in the spectral ratio between T2DM and HC were primarily driven by
658 reduced power in higher (α+β) frequencies in T2DM, without a strong increase in low-frequency
659 (δ+θ) power. If reduction in α-power indexes decreased functional inhibition relevant for
660 cognitive performance, then this may be prodromal in T2DM of subsequent increase in low-
661 frequency activity and accelerated cognitive decline. Unfortunately, due to the single time-
662 point/cross-sectional nature of the current study, the results cannot provide evidence as to the
663 existence of any causal link between T2DM and AD. It is crucial to acknowledge that the causal
664 factors underlying cognitive impairments may not be shared across the disorders; hence, we
665 cannot yet ascribe the EEG differences to a single underlying cause. Future longitudinal,
666 prospective studies are however warranted given existing epidemiologic data and the reported

667 cross-sectional findings here. Longitudinal measurements of EEG power and
668 neuropsychological performance in individuals with T2DM could test the prognostic power of
669 EEG changes in terms of subsequent cognitive decline, including progression to AD (Gispen
670 and Biessels, 2000; Stewart and Liolitsa, 1999).

671 Additional limitations of the current study include a lack of older participants, particularly
672 in the T2DM and HC groups. Future studies should look to recruit from a wider range of older
673 adults. It is important to note that, despite no individuals scoring as clinically impaired on the
674 MMSE, we were unable to fully rule out the possibility of pre-clinical AD being present in the HC
675 and T2DM groups. It would also be of benefit to collect more potentially relevant demographic
676 details which were not available here, including smoking status, comorbid psychiatric
677 symptomology and time since diagnosis. Additional information regarding medication use might
678 be of particular value given that T2DM treated with medications may not experience equivalent
679 neurocognitive consequences to those controlling the disease through exercise and diet (Walker
680 and Harrison, 2015; Ngandu et al., 2015). Furthermore, we did not consider the potential
681 association between γ-band (~30-100 Hz) oscillations and cognitive function in either T2DM or
682 AD, despite previous research suggesting γ-band activity to be cognitively relevant (van
683 Deursen et al., 2008; Başar et al., 2016). We chose not to include EEG-measured γ because it
684 is often contaminated by muscle (Whitham et al., 2007) and eye-movement artifacts (Yuval-
685 Greenberg et al., 2008). An optimal approach to investigate pathophysiological signatures of γ
686 activity in future studies would be to employ magnetoencephalography, in which cerebral γ
687 activity can be more clearly and robustly identified than in EEG (Mandal et al., 2018).

688

689 *Conclusions*

690 Neuropsychological deficits are widespread in AD and selective in T2DM (with relative sparing
691 of executive functions). Relative to HC, AD patients had higher EEG power in lower frequencies
692 and lower power in higher frequencies across all brain regions. In contrast, patients with T2DM

showed decreases in specifically α power relative to HC restricted to the temporal regions. The ratio, (α+β)/(δ+θ), showed a continuum of differences from HC to T2DM to AD. This *Spectral power ratio* correlated with dementia severity and executive functioning in AD and learning and memory performance in HC and across all groups combined. In contrast, no relationship was found between *IAF* and cognitive function in any of the three groups. Shift in the ratio of relative power (in favor of low frequencies) within the EEG power-spectrum represents a candidate neural signature of cognitive deficits associated with aging-related diseases including AD and T2DM.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

This study was primarily funded by the National Institutes of Health (NIH R21 NS082870). A.P.-L. was also supported in part by the Sidney R. Baer Jr. Foundation, the NIH (R01HD069776, R01NS073601, R21 MH099196, R21 NS085491, R21 HD07616), Harvard Catalyst | The Harvard Clinical and Translational Science Center (NCRR and the NCATS NIH, UL1 RR025758), the Football Players Health Study at Harvard University, and by the Defense Advanced Research Projects Agency (DARPA) via HR001117S0030. C.S.Y.B. was also supported by the Economic and Social Research Council (UK) (ES/I02395X/1), the Experimental Psychology Society (UK) and the Guarantors of Brain (UK). E.S. is partially supported by the Office of the Director of National Intelligence (ODNI), Intelligence Advanced Research Projects Activity (IARPA), via 2014-13121700007, by the Beth Israel Deaconess Medical Center (BIDMC) via the Chief Academic Officer (CAO) grant 2017, and by the Defense Advanced Research Projects Agency (DARPA) via HR001117S0030, and the NIH (P01 AG031720-06A1, R01 MH117063-01, R01 AG060981-01). M.M.S. is supported by the CURE

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(Citizens United for Research in Epilepsy) foundation, the Football Players Health Study (FPHS) at Harvard University, and the NIH (R01 MH115949, R01AG060987, R01 NS073601, P01 AG031720-06A1). The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, the National Institutes of Health, DARPA, IARPA, ODNI, BIDMC, or the Sidney R. Baer Jr. Foundation.

The authors thank E. Seligson, N. Atkinson, and S. Saxena for their assistance in data collection, and A. Connor and J. Macone for regulatory and compliance oversight and assistance with evaluation of participant health and medical history.

Disclosures

A.P.-L. serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Cognito, Constant Therapy, and Neosync; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging. E.S. serves on the scientific advisory boards for EBNeuro Ltd and Neuroelectrics, and is listed as an inventor on issued and pending patents on the integration of non-invasive brain stimulation with neuroimaging data for therapeutic applications in neurodegenerative disorders and brain tumors

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Figure Legends

Figure 1. *Whole-brain analysis of relative power.* **A.** *F*-ratios associated with between-group mass univariate analyses of variance (ANOVAs) comparing relative electroencephalography (EEG) power between Alzheimer's disease (AD), Type-2 diabetes mellitus (T2DM), and healthy controls (HC) across all electrodes (y-axis) and frequencies (x-axis). The solid black contour represents data points surviving cluster-based multiple comparison correction. **B.** Topographic representation of the *F*-ratios averaged across the significant frequencies. **C.** Mean power spectra (with 95% confidence intervals; CI) for each group separately at the electrode (CP6) for which group differences were maximal. Alpha/beta power showed a linear decrease across groups, being highest for HC and lowest for AD with T2DM having intermediate values whereas delta/theta power showed a linear increase across groups. **D-F**. *T*-values associated with follow-up tests comparing relative EEG power between each pair of groups separately. Solid black contours indicate data points surviving cluster-correction. **G-H**. Topographic representation of the *t*-values associated with the respective significant effects. Significant electrodes are highlighted in gray.

Figure 2. *Spectral Power Ratio.* Figure shows the age-adjusted comparison across groups of the Spectral Power Ratio, (α+β)/(δ+θ), estimated from each cortical region of interest (ROI). Tukey's Honestly Significant Difference post hoc tests demonstrated that (α+β)/(δ+θ) was lower in Alzheimer's disease (AD) than in Healthy Controls (HC) across all ROIs (*p* values < 0.001) and lower than Type-2 Diabetes (T2DM) in all but the *Posterior* ROI (*p* values = 0.0499–0.063). T2DM was lower than HC across all ROIs though this difference did not reach significance (*p values* = 0.064–0.136). Data shown represent the least squared means and standard deviations derived from the linear regression models.

Figure 3. *Group analysis and post-hoc comparisons of cognitive measures adjusted for age.* All data represent least squared means and standard error. Individual neuropsychological tests (x-axis) are shown grouped by cognitive domain. Scores (y-axis) were z-normalized and inverted (if necessary) so higher numbers reflect better performance/function. Following the first omnibus multivariate analysis of variance (MANOVA-1), group performance on individual tests was assessed using separate multiple linear regression analyses with age as a covariate. All results survived a 5% false discovery rate (FDR). In general, there was a continuum of deficits with healthy controls (HC) scoring higher than Type-2 diabetics (T2DM), who performed better than Alzheimer's disease (AD). Post-hoc pairwise comparisons were conducted with Tukey's honestly significant difference (HSD) tests. Three patterns were observed: (§) all three groups were significantly different; (†) AD scored significantly worse than both HC and T2DM, which were equivalent to each other; (^) HC were significantly better than AD, with T2DM not significantly different from either group. *Additional abbreviations*. Alzheimer's disease Assessment Scale-Cognitive subscale (ADAS-Cog); Activities of Daily Living (ADLs); Digit Symbol Substitution Test (DSST); Trail Making Test (TMT); Rey Auditory Verbal Learning Test (RAVLT); Geriatric Depression Scale (GDS).

Figure 4. *Relationship between electroencephalography (EEG) Spectral power ratio and cognitive function.* Z-normalized scores (higher score indicates better performance) from individual neuropsychological tests were averaged together to form three domains: **A.** *Learning & memory* (Rey Auditory Verbal Learning Test, Logical Memory Story); **B.** *Dementia severity* (Alzheimer's disease Assessment Scale-Cognitive subscale, Activities of Daily Living); **C.** *Executive function* (Digit Symbol Substitution Test, Semantic fluency, Trail Making, Digit Span forward and backward). Computed averages were related to the Spectral Power Ratio (α+β)/(δ+θ) and plotted separately for the three groups. In healthy controls (HC), higher (α+β)/(δ+θ) was significantly associated with better *Learning & memory* performance (p = 0.018,

uncorrected). In Alzheimer's disease (AD), higher (α+β)/(δ+θ) was significantly associated with better *Dementia severity* and *Executive function* (*p's* < 0.05, uncorrected). By contrast, no significant relationships were observed in the Type-2 diabetes mellitus (T2DM) group (*p*'s > 0.1).

Figure 5. *Group analysis of Dominant posterior frequencies.* **A**. Individual frequency between 5-15 Hz with the highest power density across all posterior electrodes (*Dominant posterior frequency*) as a function of group (Healthy controls (HC), Type-2 diabetes mellitus (T2DM) and Alzheimer's disease (AD)). **B.** Power density at the *Dominant posterior frequency* (averaged over the peak frequency ± 2 Hz) as a function of group. Colored dots denote individual participants, white dots denote group medians and background fills represent kernel density estimates.

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Table Legends

Table 1. *Results of Multivariate Analyses of Variance (MANOVAs).* In MANOVA-1, the dependent variables included z-normalized, rectified scores on the Alzheimer's disease Assessment Scale-Cognitive Subscale, Activities of Daily Living, Digit Symbol Substitution Test, Semantic Fluency Test, Trail Making Test time and errors (difference Part B-Part A), Digit Span length forward and backward, Rey Auditory Verbal Learning Test (learning, delayed recall, delayed recognition), Logical Memory story (immediate and delayed recall), Boston Naming Test, and Geriatric Depression Scale. In MANOVA-2, the dependent variables include the averaged Z-scores of the three cognitive domains (Learning & memory, Dementia severity, Executive function). EEG refers to a whole-brain averaged power ratio [(alpha + beta)/(delta + theta)] obtained from eyes-closed resting-state electroencephalography.

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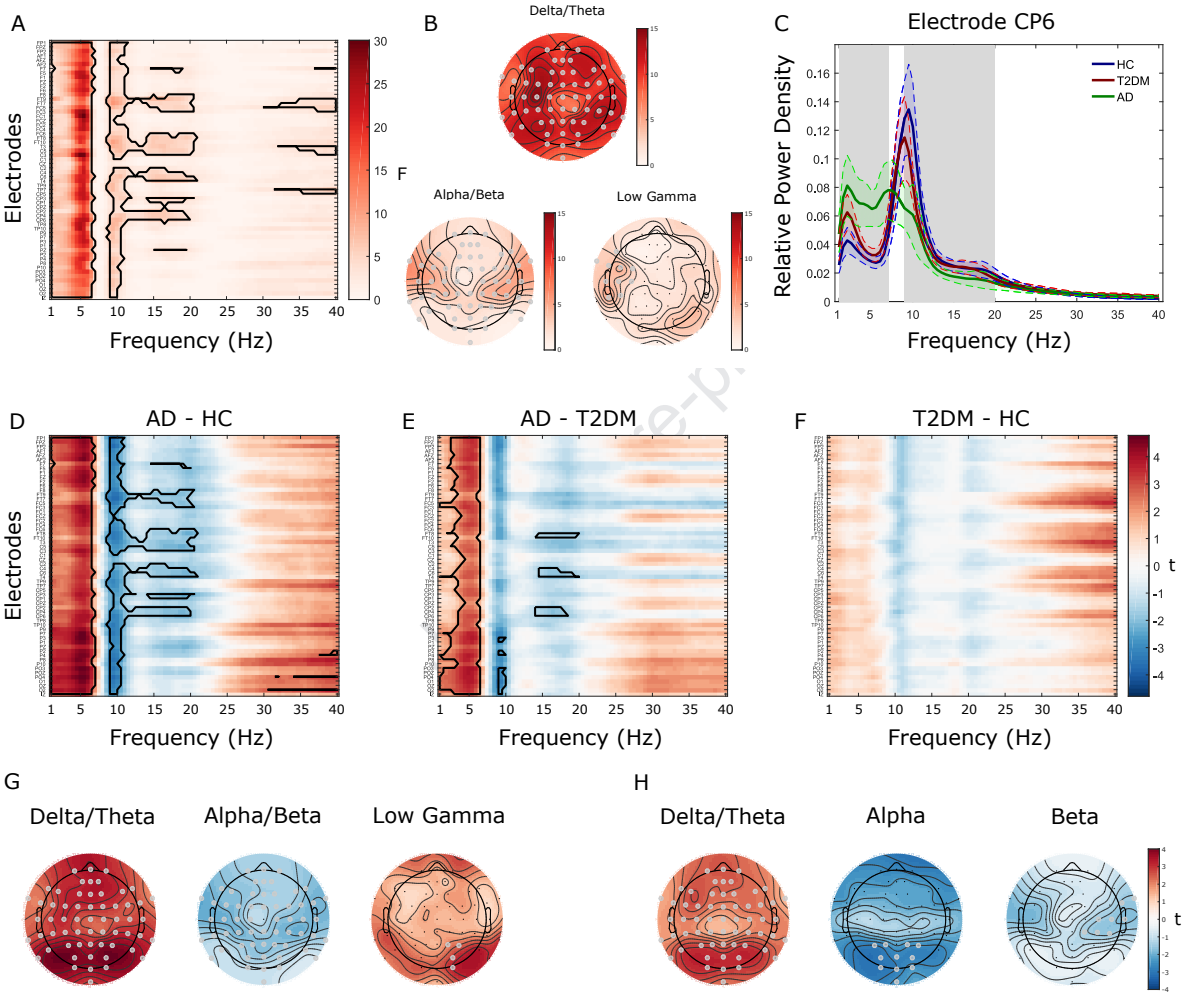
A
Electrodes
Frequency (Hz)
B
Delta/Theta
Alpha/Beta
Low Gamma
C
Electrode CP6
HC
T2DM
AD
Relative Power Density
Frequency (Hz)
D
AD - HC
Electrodes
Frequency (Hz)
E
AD - T2DM
Frequency (Hz)
F
T2DM - HC
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Delta/Theta
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Low Gamma
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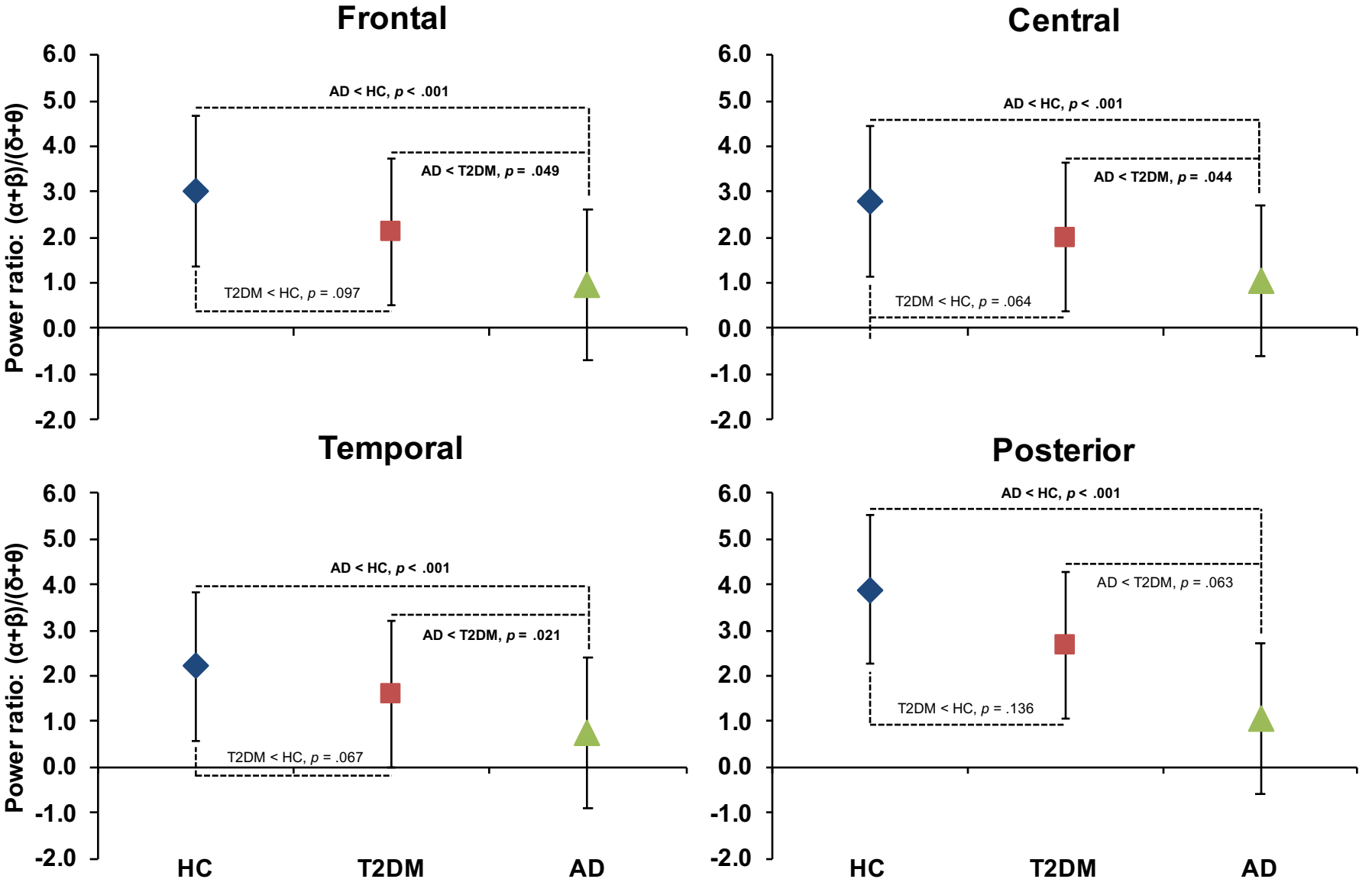
Frontal
Central
Temporal
Posterior
Power ratio: (α+β)/(δ+θ)
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
-2.0
AD < HC, p < .001
AD < T2DM, p = .049
T2DM < HC, p = .097
AD < HC, p < .001
AD < T2DM, p = .044
T2DM < HC, p = .064
AD < HC, p < .001
AD < T2DM, p = .021
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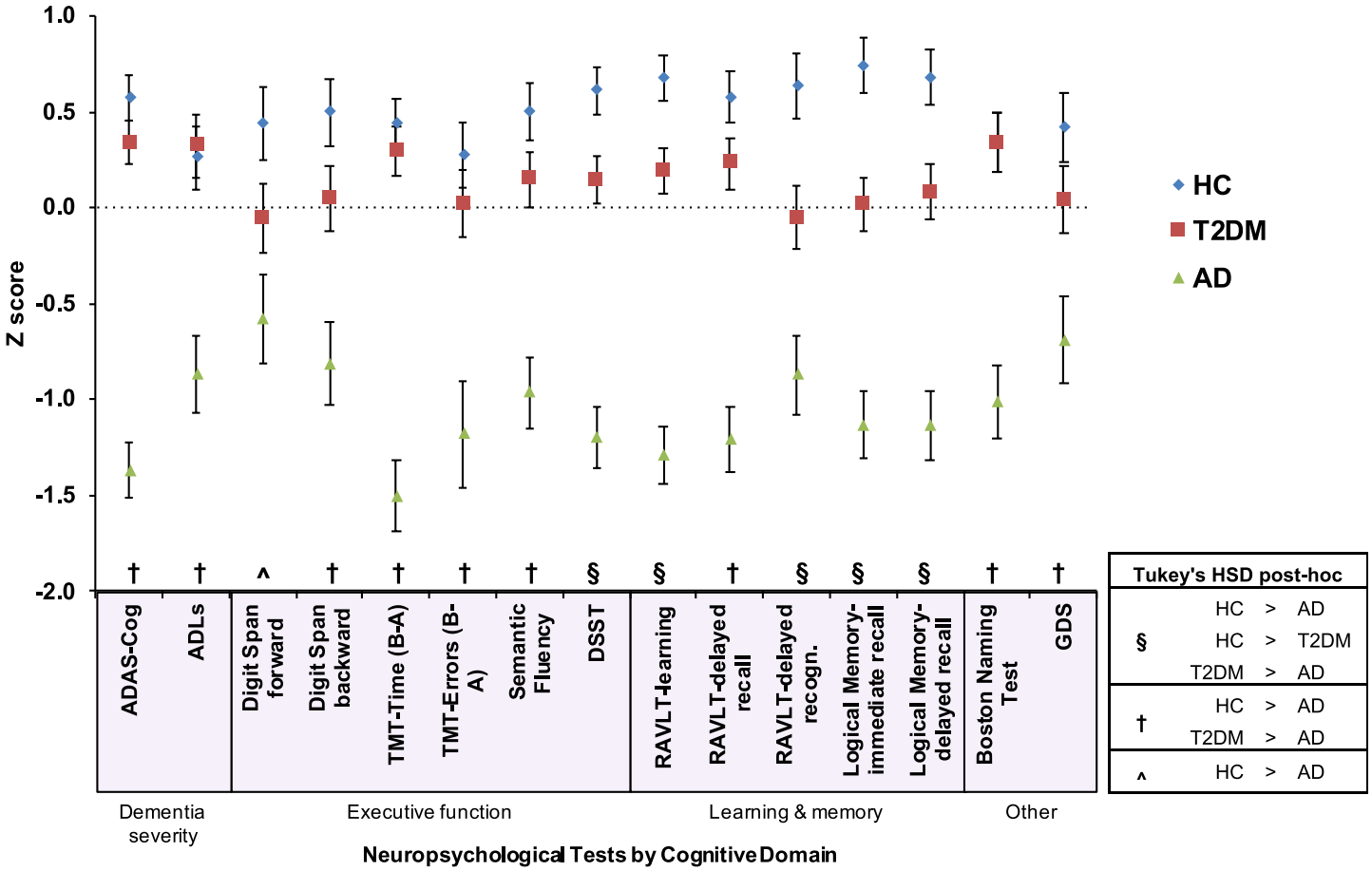
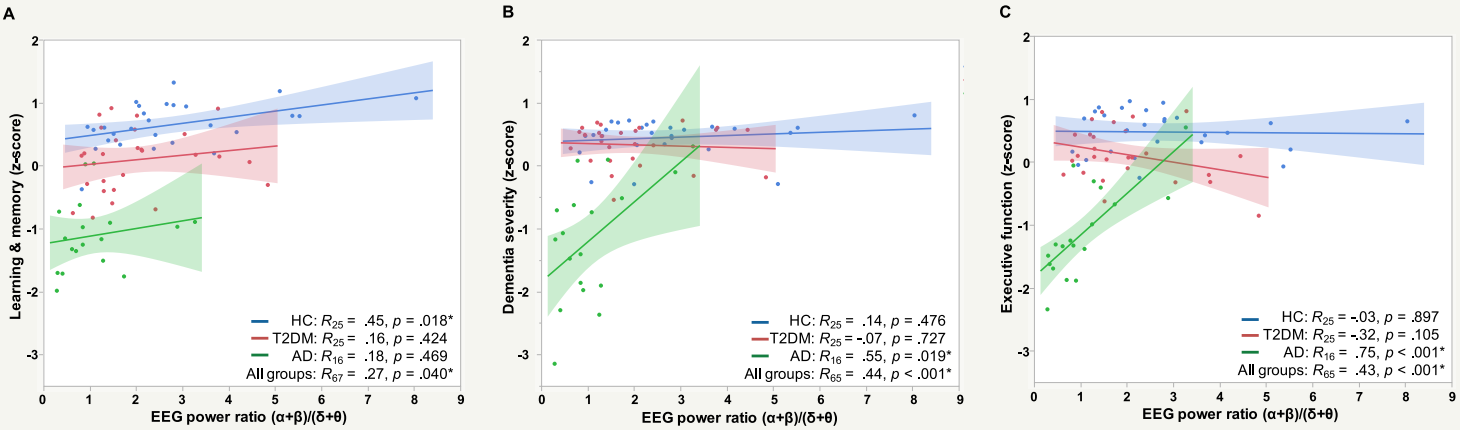
AD < HC, p < .001
AD < T2DM, p = .063
T2DM < HC, p = .136
HC
T2DM
AD

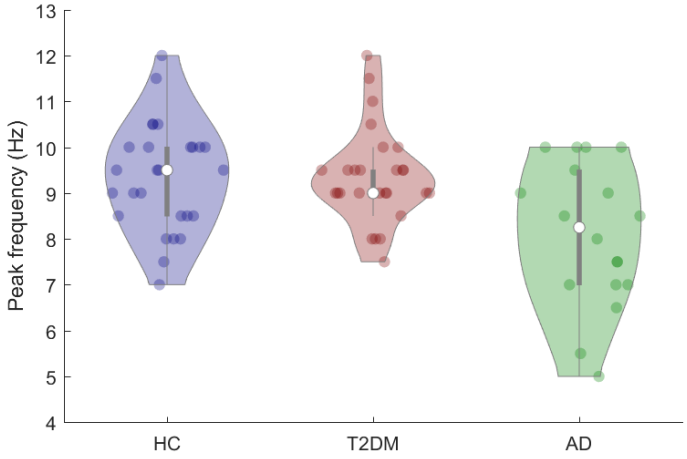

1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Z score
HC
T2DM
AD
† † ^ † † † † § § † § § § † †
ADAS-Cog
ADLs
Digit Span forward
Digit Span backward
TMT-Time (B-A)
TMT-Errors (B-A)
Semantic Fluency
DSST
RAVLT-learning
RAVLT-delayed recall
RAVLT-delayed recogn.
Logical Memory-immediate recall
Logical Memory-delayed recall
Boston Naming Test
GDS
Dementia severity
Executive function
Learning & memory
Other
Neuropsychological Tests by Cognitive Domain
Tukey's HSD post-hoc
§ HC > AD
HC > T2DM
T2DM > AD
† HC > AD
T2DM > AD
^ HC > AD

Journal Pr

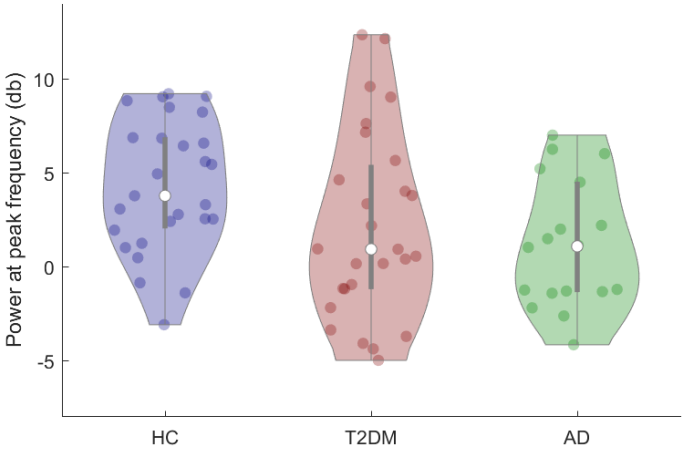


Journal Pre-proof

A



B



Journal Pre-proof